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Direct enantioselective aldol reactions catalyzed by calix[4]arene-based L-proline derivatives in the water

Serkan Eymur, Ezgi Akceylan, Ozlem Sahin, Arzu Uyanik, Mustafa Yilmaz *

Selcuk University, Department of Chemistry, 42031 Konya, Turkey

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Two novel *p-tert*-butylcalix[4]arene-based chiral organocatalysts derived from L-proline have been developed to catalyze direct aldol reactions between cyclohexanone and aromatic aldehydes in water. Under the optimal conditions, high yields (up to 95%), enantioselectivities (up to 90%), and moderate diastereoselectivities (up to 65:35) were obtained. Considering the catalytic inefficiency of sole proline for the aldol reaction in water, these results clearly display the enormous effect of the hydrophobic part of calix[4]arene of compound **A**.

1. Introduction

The aldol reaction has been one of the most efficient methods for C–C bond forming reactions, creating β-hydroxy ketones, which are involved in the structure of many biologically important compounds that also pertain to pharmaceutical fields.[1] In particular, asymmetric aldol reactions have gained great attention in the past few decades.[2] Following the pioneering work of the proline-catalyzed asymmetric direct aldol reaction by List et al. in the early 2000s,[3] organocatalyzed asymmetric aldol reactions were professed to be a powerful tool in asymmetric organic synthesis. Since the inspiration of these studies originated from nature's C–C bond forming reactions utilizing class I aldolase enzymes,[4] the development of enantioselective transformations using water as a reaction medium has attracted great interest in the scientific community because of the its low cost, safety, and environmentally benign nature.[5] Unfortunately, while proline catalyzes direct aldol reactions with high enantioselectivity in polar organic solvents, almost racemic products were obtained in the presence of water or a buffer solution because water interferes with the organocatalysts and disturbs hydrogen bonds as well as other polar interactions.[6] In this context, much attention has already been given to the problem in order to find new methodologies including new types of organocatalysts for improving the enantioselectivities of the aldol reaction products in water.[5,7]

In 2006, Barbas and Hayashi independently reported the combined use of proline-derived chiral catalyst bearing hydrophobic alkyl chains and an acid to perform a direct aldol reaction in the presence of water.[8] They postulated that a small organic catalyst with suitable large hydrophobic substituents should assemble with hydrophobic reactants in water and diminish contacts between bulk water and the reaction transition states. Since then, it has generally been thought that good efficiencies in water may be accomplished within 'hydrophobic activation', linking proline derivatives to suitable hydrophobic moieties.[9]

Calixarenes, with their unique three-dimensional surface and conformationally rigid structure, are one of the best-known macrocyclic organic host compounds of phenolic units linked by methylene or groups at the 2,6-positions. The capability of being modified at either the upper and/or lower rims of the molecular skeleton has made this class of macrocyclic compounds increasingly attractive for the scientists involved in the field of supramolecular chemistry.[10] Considering the intramolecular hydrophobic cavities of calixarenes, we note that it is crucial for catalysis that a hydrophobic platform is required, which may allow reaction to proceed in the presence of water. Once the possibilities of modification for these macromolecules make them suitable for asymmetric reactions, it is not unexpected that calixarene-based organocatalysts have been developed for a direct aldol reaction in aqueous solutions.[11] However, to the best of our knowledge a direct aldol reaction catalyzed by calixarene bearing proline moiety in the presence of a large amount of water has not been yet described.

We believe that the development of proline derivatives with large hydrophobic moieties capable of catalyzing enantioselective aldol reactions using water as a solvent is still attracting great interest. Taking into account our longstanding research into

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* Corresponding author. Tel.: +90 332 2233873; fax: +90 332 2410520; e-mail address: myilmaz42@yahoo.com (M. Yilmaz).

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calixarenes,[10e,12] herein, we thought it of interest to design a novel class of organocatalysts by coupling L-proline with calix[4]arenes as represented in Fig. 1.

We envisioned that the special hydrophobic cavities of such derivatives would facilitate the aldol reaction in water. The role played by the hydrophobic effect of calix[4]arene on the conversion and stereoselectivity of the reaction is studied here and the results discussed.

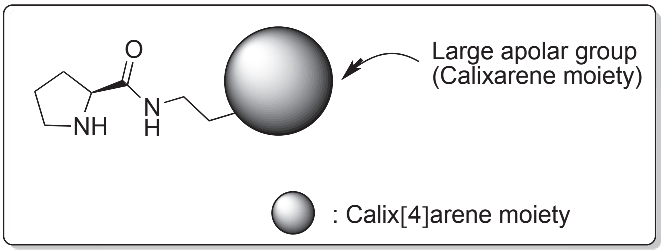

Fig. 1. Schematic representation of organocatalysts examined in this study.

2. Results and discussions

2.1. Catalyst preparation

Catalysts **A** and **B** were readily prepared according to routine methods (Scheme 1).

First, *tert*-butylcalix[4]arene **1** was reacted with 3-bromopropyl phthalimide in the presence of K_2CO_3 to give bis(3-phthalimidopropoxy)calix[4]arene **2**.[13] The phthalimido groups were removed with hydrazine hydrate in EtOH to result in bis(3-aminopropoxy)calix[4]arene **3**.[13] The Boc-protected L-proline was reacted with bis(3-aminopropoxy)calix[4]arene by *N*,*N*′-dicyclohexylcarbodiimide (DCC) coupling method to result in compound **4** in 73% yield. Then direct deprotection of the Boc group by trifluoroacetic acid (TFA) in dichloromethane quantitatively resulted in the catalyst **A** in 70% yield. Catalyst **B** was synthesized using an acid chloride method. The reaction of acid chloride **6**[14] with *N*-(2-aminoethyl)-*N*′-(*tert*-butoxycarbonyl)-L-prolinamide[15] results in the corresponding diamide derivative of calix[4]arene **7** in 75% yield. The formation of compound **7** was confirmed by the appearance of the characteristic amide band at about 1666 cm^{-1} in the IR spectra. Catalyst **B** was finally obtained by TFA treatment with 71% yield from compound **7**. The chemical structures of these organocatalysts **A** and **B** were completely characterized by ^1H, ^{13}C NMR, and IR analyses. The conformational characteristics of calix[4]arenes were conveniently estimated by way of the splitting pattern of the ArCH_2Ar methylene protons in the ^1H and ^{13}C NMR spectra.[10] ^1H and ^{13}C NMR data showed that newly synthesized chiral *p-tert*-butylcalix[4]arene derivatives **A** and **B** are in a cone conformation.[16] A typical AB pattern was observed for the methylene bridge ArCH_2Ar protons at δ 3.33 and 4.23 ppm (J=12.9 Hz) for **A**, and δ 3.29–3.63 and 4.53 ppm (J=12.9 Hz) for **B** in ^1H NMR. The high field doublets at δ 3.33 ppm for **A** and δ 3.29–3.63 ppm for **B** were assigned to the equatorial protons of the methylene groups, whereas the low field signals at δ 4.23 ppm for **A** and 4.53 ppm for **B** were assigned to the axial protons in the ^1H NMR.

2.2. Optimization of aldol condensations

In an initial experiment, we studied the aldol reaction using cyclohexanone and *p*-nitrobenzaldehyde in the presence of organocatalysts (**A**, **B**) and water. Organic solvents were also employed as the reaction medium. The reaction conditions parameters, such as catalyst loading, amount of solvent, and temperature were firstly evaluated.

When the reaction proceeded in organic solvents, the *anti*-isomer was obtained with moderate diastereoselectivity and low conversion. Common organic solvents, such as chloroform, DMSO, acetonitrile, DMF, and ethanol were not suitable for both catalysts **A** and **B**; only low enantiomeric excess was determined within 24 h when these solvents were used (Table 1, entries 1–9). When the reaction medium was changed from organic solvents to water, we were pleased to notice an increased conversion and enantioselectivity of corresponding aldol product (Table 1, entries 10 and 11). When the reaction was performed in water with 20 mol % catalyst **A**, the formation of aldol product was observed in 90% conversion and 46% ee (Table 1, entry 10). Encouraged by the results, we next evaluated the effect of catalyst loading on reactivity and selectivity. We found that the relative amount of catalyst could be reduced to 10 mol % without significant loss in reactivity and selectivity (Table 1, entry 12). Remarkably, catalyst loadings as low as 5 mol % could also be utilized without significant loss in enantiocontrol (Table 1, entry 13).

We then investigated the effect of different amounts of water by using catalyst **A**. We selected catalyst **A** due to the faster reaction times and higher isolated yields compared to those of catalyst **B** with similar levels of selectivity. As seen in Table 2, when 440 equiv of water (1000 μL) was used, a high conversion was observed (Table 2, entry 1). Moreover, using 220 equiv of water (500 μL) gave better results both in terms of yield and stereoselectivity (Table 2, entry 2). It should be noted that a small amount of water does not interrupt the reaction at all. The reaction proceeds smoothly even in the presence of 18 equiv of water to provide nearly the same enantioselectivity (Table 2, entry 5).

In order to confirm the role of the hydrophobic calixarene platform of **A** and **B**, monomeric analog (catalyst **C**) of **A** was also prepared according to routine methods (Scheme 2). A key control reaction was carried out because more simple L-proline derivatives are known to be good catalysts for the asymmetric aldol reactions. In control experiment, low conversion and diastereoselectivity were observed by using catalyst **C** (Table 1, entry 14).

These observations all clearly demonstrate the importance of the hydrophobic part of the calix[4]arene skeletons in compounds **A** and **B** for the reaction to proceed in the presence of water. The highest enantiomeric excess was obtained by using 250 μL of water (Table 2, entry 3), and thus all further reactions were performed using this volume of water. Moreover, it was also found that good results were obtained when neat reaction conditions were employed (Table 2, entry 7).

In the literature, it has been shown that additives, bases, or acids are sometimes needed to improve the rate and enantioselectivity of the reaction by promoting the enamine formation.[17] We were then inspired to perform the enantioselective aldol reaction in the presence of additives to find out the optimal working conditions (Table 3). First benzoic acid (PhCOOH) was used as an additive because it is commonly used in aldol reactions. The reaction time was notably shortened from 24 h to 16 h when 20 mol % PhCOOH was employed (Table 3, entry 1). Acetic acid also furnished a comparable enantioselectivity of 75% under the same reaction conditions. The additive trifluoroacetic acid and PTSA were also used, but all provided low to poor conversions, as shown in entries 3 and 4 of Table 2. From the results it is clear that 20 mol % chloroacetic acid was found to be the best additive in terms of conversion as well as selectivity (Table 3, entry 6). The different amounts of chloroacetic acid were also tested, but there was no improvement of enantioselectivity as shown in entries 7 and 8 of Table 3.

2.3. Substrate scope

With these optimal conditions in hand, we next sought to investigate the scope of this asymmetric catalytic aldol reaction. All